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Rituximab-based novel strategies for the treatment of immune-mediated glomerular diseases

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Abstract

Rituximab is a monoclonal antibody to the CD20 antigen on B-cells that was initially designed and approved for the treatment of non-Hodgkin's B-cell lymphoma in 1997.

In the last 15 years, it has emerged as a potent immunosuppressant for many immune-mediated diseases, beginning initially with rheumatoid arthritis, and now extending into several other fields, including clinical nephrology. Based on recent large clinical trials, it is FDA-approved for the treatment of ANCA-associated vasculitis and continues to be studied in off-label usage for many glomerular diseases, including membranous nephropathy, lupus nephritis, and mixed cryoglobulinemia. It has been used as a treatment in nephrotic syndrome in children and adults, including both minimal change disease and focal segmental glomerulosclerosis. Given its efficacy, tolerability and safety profile in comparison to more conventional treatment regimens, RTX is rapidly emerging as a critical treatment modality in glomerular disease.

Keywords

Rituximab; ANCA; Vasculitis; Membranous nephropathy; Lupus nephritis; Mixed cryoglobulinemia; Focal segmental glomerulosclerosis; Minimal change disease

1. Introduction

Rituximab (RTX) is a genetically engineered chimeric murine-human monoclonal antibody that binds to CD20, which is expressed on human B cells and at low levels on a small subset of T cells [1]. Mechanisms of depletion include antibody- and complement-mediated cytotoxicity [2], the latter likely being involved in infusion reactions [3]. Some non-circulating tissue B cells seem to bind RTX but are not depleted [4]. The role of tissue-restricted depletion-refractory B cells and CD20 expressing T cell subsets in influencing RTX responsiveness is under investigation. RTX has an acceptable safety profile. The incidence of serious infections was quantified in a cohort of 1053 rheumatoid arthritis patients as 5.4 events per 100 patient-years [5]. Fatal infections were invariably associated with the combination of RTX with conventional immunosuppressants, including azathioprine, mycophenolate mofetil and cyclophosphamide [6]. Pre-medication with steroids, anti-histamine drugs and paracetamol actually does reduce the risk of intolerance reactions.

Research into the underlying mechanisms of several immune-mediated glomerular diseases has revealed the importance of auto-antibodies in these disease processes. In diseases such ANCA-associated vasculitis (AAV) [7], mixed cryoglobulinemia [8], membranous nephropathy [9] and lupus nephritis [10] auto-antibodies either have been implicated in direct glomerular injury or as correlates with disease activity. Given this understanding, RTX has emerged as an exciting new therapeutic agent to treat immune-mediated renal disease, with variable success. In this review, the current state of anti-CD20 therapy in several glomerular disease processes will be discussed.

2. Anti-neutrophil cytoplasmic antibody (ANCA)-associated small-vessel vasculitis

AAV is a severe, progressive disease that can result in death due to multisystem organ failure [11]. Prognosis has greatly improved with the use of high-dose steroids and cyclophosphamide, though the disease process is characterized by frequent relapses within 3–5 years of initial therapy. However, a 10–20% of patients with AAV are refractory to conventional therapy or experience dose-limiting side effects [12]. Patients undergoing standard immunosuppressive therapy are susceptible to cumulative toxicity derived from multiple courses of therapy, in addition to the damage related to the disease itself. Finally, even in patients who achieve remission, quality of life often remains compromised due to the devastating effects of the current therapies [13]. Infertility and malignancies (especially in long-term treatment) in the young patient, and leukopenia and infections in the elderly make standard immunosuppressive treatment unappealing.

RTX was initially investigated as an optional therapy in small vessel idiopathic systemic angiitis because of the need for efficacious therapies for patients who are refractory or intolerant to standard therapy. B-lymphocytes have long been implicated in the pathogenesis of AAV [14] and the number of activated B lymphocytes has been shown to correlate with disease activity and severity. The first use of RTX to induce remission in a patient with refractory and frequently relapsing AAV was reported by Specks et al. in 2001 [15]. Subsequently, a number of reports documented the clinical benefits of RTX given in addition to cyclophosphamide, methotrexate, azathioprine or mycophenolate mofetil [11], [16], [17] and [18]. In general, clinical remission has been reported in about 80% of cases by 6 months [19] and one of the significant benefits is that patients can often be titrated off other immunosuppressants, including corticosteroids, after receiving RTX [11]. This favourable profile was confirmed in a retrospective data collection performed on 65 patients receiving RTX for refractory AAV at four centres in the UK [20]. Remission occurred in 49 of the 65 patients (75%), while 15 patients experienced partial remission. Thirty-eight patients received a second course of RTX and among those re-treated, complete remission was induced or maintained in 32 patients (84%).

Based on the results of open-label studies, two randomized studies were designed to test the efficacy of RTX as induction therapy compared to standard treatment with cyclophosphamide [21] and [22]. The RITUXVAS (RTX versus Cyclophosphamide in ANCA-Associated Renal Vasculitis) study [21] randomized 44 patients with AAV and renal involvement to either receive RTX 375 mg/m² weekly for 4 doses in addition to steroids and 2 doses of intravenous cyclophosphamide or to conventional therapy, including steroids, cyclophosphamide for 3–6 months, and azathioprine maintenance. Remission rates (76% in RTX vs. 82% in conventional therapy) and adverse events (42% in RTX vs. 36% in conventional therapy) were similar in both groups. A larger trial, Rituximab vs. Cyclophosphamide for ANCA-Associated Vasculitis (RAVE), was a multi-centre, randomized, double-blind, double-placebo controlled, non-inferiority study that was designed to test the ability of RTX to induce remission in patients with AAV [22]. There were 197 enrolled patients and there were equal numbers of newly diagnosed and relapsed cases. The experimental arm received RTX 375 mg/m² weekly for 4 doses combined with steroids that were tapered to 0 over 6 months, and the control arm received cyclophosphamide, followed by azathioprine maintenance. Remission was induced in 64% of those treated with RTX vs. 53% in those treated with cyclophosphamide and this was significant for the non-inferiority outcome. Interestingly, RTX was more effective for relapsing disease (67% vs. 42%, $P < 0.01$). Based on these results, the FDA approved the use of RTX for AAV in 2011.

With regard to long-term effects, preliminary analysis of the 18-month follow-up in RAVE shows that a single course of RTX may be sufficient to induce long-term remission and prevent relapse. This treatment strategy would have the added benefit of limiting side effects in the long-term [23]. A recent open-label study specifically focused on the durability of the treatment effect in a small cohort of 11 difficult patients (7 with renal involvement) with micropolyangiitis with or without a granulomatous phenotype who were intolerant or refractory to conventional therapies [24]. All patients received RTX (4 weekly doses of 375 mg/m² and 2 more doses at 1-month intervals). No additional immunosuppressive maintenance therapy was administered. Significant decreases in levels of serum creatinine and proteinuria as well as in the Birmingham Vasculitis Activity Score were observed. None of the patients relapsed during a 36 month follow-up.

The use of RTX as a maintenance therapy was recently described in a retrospective study by Smith et al [25] based on their single-centre experience of patients with refractory and relapsing AAV. They examined three cohorts of patients — Group A (n = 28) received RTX induction and RTX again at the time of relapse, Group B (n = 19) were treated with RTX induction and routine re-treatment with 1 g every 6 months and Group C (n = 19) were Group A patients who relapsed and then were switched to the routine re-treatment arm after it was introduced in 2006. Overall, they had a 93% initial response rate in Group A, 96% in Group B and 95% in Group C and additional immunosuppressants were withdrawn in the majority of patients. At 2 years, 73% of Group A patients had relapsed, whereas only 12% of Group B and 11% of Group C patients had relapsed. Longer follow-up was available for some patients and for those with 48 months of follow-up, 81% of Group A, 26% of Group B and 39% of Group C had relapsed. Interestingly, the time to relapse in the routine re-treatment arms were 29 months and 34.5 months in Groups B and C, respectively, versus 12 months in Group A. The authors speculate that repeating RTX dosing when the disease is inactive is more likely to remove auto-reactive B cells and cause longer remissions. They did not find a reliable relationship between degree of B cell depletion, ANCA levels and relapses, however, they did notice that the majority of relapses in the routine re-treatment arms occurred in the 2 months preceding the next dose of RTX. Conversely, in another recent retrospective study by Cartin-Ceba et al [26] on the ten-year experience of the Mayo Clinic (2000-2010), examination of the outcomes of 53 patients with relapsing AAV who received at least 2 courses of RTX revealed that all relapses were accompanied by increasing ANCA levels (with the exception of the one ANCA-negative patient) and with the reconstitution of B cells, defined as > 20 CD19 cells/μL. The majority of patients were re-treated with RTX pre-emptively (64%) based on serial ANCA measurements and B cell monitoring. The results of these two studies suggest that RTX for chronically relapsing AAV is effective, but whether patients should be treated with a standing RTX re-treatment regimen or whether re-treatment should be guided by ANCA and B lymphocyte levels is yet to be determined.

3. Lupus nephritis

Systemic Lupus Erythematosus (SLE) is a multisystem autoimmune disease characterized by the production of auto-antibodies against a variety of self antigens. B cells play a central role in SLE. Targeting the B cell compartment is therefore an attractive alternative to currently available therapies. RTX has been investigated in SLE because of the potentially serious toxicity of immunosuppressive agents currently in use. Some trials in adults and children with SLE suggested that RTX given in combination with other immunosuppressive drugs may improve several manifestations of SLE, including skin rash, alopecia, arthritis, haemolytic anaemia and thrombocytopenia [27], [28], [29] and [30]. However, an initial phase I/II trial in moderate to severe active extrarenal lupus failed to show that RTX was superior to placebo when added to standard therapy [31]. A larger phase III study to evaluate the efficacy of RTX in treating proliferative lupus nephritis (LUNAR) was published in 2012. The study enrolled 144 patients with class

III/IV lupus nephritis and randomized them to RTX and standard therapy, including mycophenolate mofetil and steroids, or placebo and standard therapy. The response rate in the RTX arm was 57% versus 46% in the standard therapy arm and this was not statistically significant, though there was a trend toward benefit in the African-American and Hispanic subset of patients [32]. Background treatment, concomitant therapies and ethnic factors have been emphasized as relevant factors in explaining the different outcomes of patients recruited in controlled and uncontrolled studies [33], [34] and [35]. Open-label studies focused on patients who were either refractory or intolerant to standard immunosuppressants and who were unlikely to be included in randomized controlled studies. For instance, in Gunnarsson's experience in 7 cyclophosphamide-resistant female patients treated with a combination of RTX and cyclophosphamide [34], the SLEDAI score and anti-dsDNA significantly dropped, while on repeat renal biopsy, improvement in the histopathological class of nephritis with a decrease in the renal activity index occurred in the majority of patients. Similarly promising results were obtained in Lu's large series in refractory patients [33]. More recently, in an uncontrolled, single centre study involving 8 SLE patients with severe multiorgan involvement who received an intensive treatment course of 4 plus 2 infusions of RTX (375 mg/m² on days # 2, 8, 15 and 22 with 2 more doses administered 1 and 2 months following the last weekly infusion), combined with two pulses of 750 mg cyclophosphamide (days # 4 and 17) and three pulses of 15 mg/kg methylprednisolone (days #1, 4 and 8) followed by oral prednisone, 50 mg for 2 weeks rapidly tapered until 5 mg in 2 months, proteinuria remarkably improved in the nephritic patients, and the SLEDAI score dropped from 17.3 (12–27) before therapy to 3.1 (1–5) after RTX [36].

4. Mixed cryoglobulinemia-associated glomerulonephritis

Hepatitis C virus (HCV) infection is known to be implicated in the majority of cases of mixed cryoglobulinemia (MC), previously defined as “essential.” MC is an example of how an autoimmune process becomes independent from the infectious agent triggering the initial steps of the pathogenesis of the disease and assumes a predominant role in the development of the disorder. Encouraging results have been obtained in open-label studies and single case reports. RTX improves or cures various clinical manifestations of MC, including fatigue, purpura and skin ulcers, arthralgias and arthritis, glomerulonephritis (in about 90% of cases), peripheral neuropathy (in about 75% of cases), and hyperviscosity syndrome [37], [38], [39], [40], [41], [42], [43], [44], [45], [46], [47], [48], [49], [50] and [51]. RTX was also reported to be effective in some life-threatening cases of gastrointestinal vasculitis [43].

Glomerulonephritis responded within the first three months of treatment. Skin ulcers usually improved within three months after the beginning of RTX therapy, but complete healing required a longer time [37], [38] and [40]. Both sensory and motor neuropathy improved 1–5 months after RTX [38], [40], [41] and [51]. Interestingly, RTX therapy exerted a steroid-sparing effect on MC [37], and some patients, including cases with active nephritis, were treated ab initio without steroids [39]. RTX also restored some MC-related immune abnormalities [52]. These effects are concomitant with the disappearance of bone marrow B cell clonal expansion [39] and [53]. A multi-centre, randomized, long-term controlled trial was recently performed in MC patients who failed or were not eligible for antiviral therapy. This trial compared RTX (without or with low-dose steroids) to a conventional immunosuppressive treatment including corticosteroids, cyclophosphamide, azathioprine, or plasma exchange. This trial documented the superiority of RTX over standard therapy [54]. Duration of response to RTX of MC manifestations is difficult to define due to the lack of long-term follow-up data in most studies. Short-term relapses, within 3–4 months after RTX treatment, occurred in a minority of patients, while long-term responses, lasting more than one year, were the most frequent outcomes. A proposed strategy, in an attempt to delay the relapses, is to administer two more infusions of RTX 1 and 2 months after the standard four week course (4 plus 2 infusion protocol) [39]. Re-treatment with RTX at disease relapse again proved to be effective in most cases

[37], [40] and [43] . Maintenance therapy with RTX is rarely reported in MC, and may be taken into consideration in patients with severe chronic nephritic syndrome or abdominal vasculitis. Short-term infusion reactions after RTX administration do not appear to be more frequent in MC than in other immune-mediated disorders, including rheumatoid arthritis. The risk of serum sickness is negligible. Patients with high cryocrit could experience severe flares of vasculitis within two days after RTX infusion, especially if the rheumatoid arthritis scheme (1 g i.v. given 2 weeks apart) of administration is given. Plasma exchange before RTX administration has been suggested in patients with high cryocrit levels [55]. RTX treatment does not significantly affect HCV viral load or parameters of liver impairment. Presently, there are no data supporting a substantial risk of liver toxicity directly caused by RTX or due to HCV reactivation, even in the long term. Moreover, RTX treatment was administered to MC patients with liver cirrhosis who showed an improvement in MC symptoms and in liver function, despite a transient increase in serum HCV RNA [49]. Except for transplanted patients, no life-threatening infections have been reported in typical HCV-related MC after RTX administration. While antiviral drugs administered with RTX may possibly be synergic [44], [56], [57], [58] and [59], they multiply the adverse effects thereby making treatment poorly tolerated. Until recently, it was believed that staggered administration after a critical phase of vasculitis was mandatory in order to avoid the risk of exacerbating HCV infection, but in most cases it is probably unnecessary [60].

5. Idiopathic membranous nephropathy

Membranous nephropathy is the most common cause of nephrotic syndrome in Caucasians and an important cause of end-stage renal disease in the adult population [61]. Recent research by Beck et al has shown that 70% of patients with idiopathic membranous nephropathy have an auto-antibody to the M-type phospholipase A2 receptor (PLA2R) that is present on podocytes [9]. Initial studies of RTX in patients with membranous nephropathy demonstrated a variable response, though there were some subjects that had significant improvement [62]. Like many of the other disease processes described, current treatment strategies include steroids, cyclophosphamide and other immunosuppressants, such as calcineurin inhibitors and mycophenolate mofetil. Therefore, the promise of RTX in membranous nephropathy has led to further studies. Fervenza et al, in a 2008 study [63], treated 15 patients with idiopathic membranous nephropathy with RTX 1 G 2 weeks apart and followed their clinical course for 1 year. Overall, there was a 48% reduction in proteinuria and 2 patients had a CR, while 6 additional patients had a PR. B-cell counts started to recover at 3 months, and ten patients were retreated at 6 months when their B-cell population repopulated. The authors measured RTX levels and showed that levels were lower than in patients with RA at the same time point, suggesting that proteinuria may decrease the amount of RTX in the blood. However, there was no correlation with drug level and response to treatment. A subsequent study used the 375 mg/m² weekly for 4 dose regimen at 0 and 6 months and 50% of patients had either CR or PR at 1 year and 80% had CR or PR at 2 years [64]. The response rates were similar to the prior study, but there was a lower incidence of human anti-chimeric antibodies (HACAs) using the second treatment regimen. In a prospective study of 100 consecutive patients with idiopathic membranous nephropathy, Ruggenenti et al [65] examined the reduction in proteinuria after a median of 30 months of follow-up in patients treated with RTX. They found a steady decrease in proteinuria, from 10.6 ± 6.4 g/24 h at baseline to 4.7 ± 0.5 g/24 h at 1 year, 3.0 ± 0.5 g/24 h at 2 years and 2.0 ± 0.4 g/24 h at 3 years (p < 0.05). In addition, 94% achieved CR or PR at 3 years and treatment was well-tolerated. There were 6 patients that did reach end-stage renal disease despite treatment. There is currently an ongoing, multi-centre, randomized control study comparing the use of RTX versus cyclosporine in the treatment of membranous nephropathy (ClinicalTrials.gov Identifier: NCT01180036).

With the discovery of the anti-PLA2R antibody, there has been considerable interest into whether the level can be used clinically to predict and monitor response. In a study by Beck et al [66] in 2011, 71% of the 35 patients with membranous nephropathy were positive for the antibody at study onset. After treatment with RTX, the amount of anti-PLA2R antibody either decreased or disappeared in 68% of patients at 12 months. Among those patients with a decrease in the antibody, 59% achieved CR or PR at 1 year and 88% at 2 years versus no patients at 1 year and 33% at 2 years in those with persistent anti-PLA2R antibody. In addition, the decrease in antibody preceded the reduction in proteinuria by several months. The presence or absence of the antibody did not predict who would respond to therapy, however, and therefore should not influence whether a patient should receive RTX. There is also evidence that additional podocyte antigens, such as neutral endopeptidase (NEP), aldose reductase (AR), SOD2 and α -enolase (α -ENO) may be the target of pathologic auto-antibodies in idiopathic membranous nephropathy [67], [68], [69] and [70]. A recent study examined the auto-antibody profile of 186 consecutive patients diagnosed with idiopathic membranous nephropathy [71], as well as of healthy controls and patients with other proteinuric diseases (FSGS and IgA nephropathy). Among patients with membranous nephropathy, 34% were positive for anti-AR, 28% for SOD2 and 43% for α -ENO ($P < 0.001$ for all comparisons). Anti-NEP did not differ between cases and normal controls. Consistent with prior studies, they did find that 60% of patients were anti-PLA2R antibody positive. Of those who were negative for anti-PLA2R, 51% had at least 1 other antibody present and only 20% of patients were completely negative for all antibodies, with most having intermediate positivity. There is ongoing research into whether additional factors, such as urinary biomarkers, may help predict the course of the disease and/or who will respond to therapy. Several authors have examined whether the measurement of low and high molecular weight urinary proteins may be helpful in determining prognosis, rate of progression and response to therapy in membranous nephropathy [72], [73], [74] and [75]. Bazzi et al [76] published a study in 2001 looking at the excretion of urinary proteins in 78 patients with membranous nephropathy. They found that urinary excretion of IgG and α 1 microglobulin at lower levels (less than 110 mg/g UCr and 33.5 mg/g UCr, respectively) could predict improvement, and that remission occurred in 100% vs. 20% using the threshold for IgG and in 77% vs. 17% using the threshold for α 1 microglobulin. In a more recent study [77], the urinary samples of 20 patients with membranous nephropathy who received treatment with RTX were studied. Urinary levels of α 1 microglobulin, retinol binding protein (RBP), albumin, IgG and fractional excretion of IgG all decreased from baseline to 12 months, while levels of IgM and fractional excretion of IgM were unchanged. By linear regression, baseline urinary IgG and fractional excretion of IgG, α 1 microglobulin and RBP, all predicted who would respond to therapy at 12 months, but none could predict response at 24 months. Further study into urinary biomarkers and anti-podocyte antibodies may help elucidate the pathogenesis of membranous nephropathy and predict who will respond to therapy.

6. Focal segmental glomerulosclerosis and minimal change disease

Idiopathic nephrotic syndrome in children encompasses several disease processes, the most important of which are minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS). While children typically respond well to steroids and are often treated empirically without a kidney biopsy, those who are steroid-dependent, steroid-resistant and/or frequent relapsers, pose a therapeutic challenge. While the underlying pathophysiology is still being actively investigated, T-cell dysfunction and various permeability factors have been implicated in the pathogenesis [78], [79] and [80]. RTX has been used with some success

in children with steroid-dependent idiopathic nephrotic syndrome, as shown in several case reports [81], [82], [83] and [84]. A randomized clinical trial of 54 children with steroid- and calcineurin inhibitor-dependent nephrotic syndrome treated with RTX versus standard therapy showed that proteinuria decreased by 70% more in the RTX arm [85]. Importantly, 63% of patients treated with RTX were drug-free at 3 months versus 3.7% in the control arm. A more recent, open-label, randomized controlled trial on the use of RTX in children with steroid-resistant nephrotic syndrome failed to demonstrate that adding RTX to prednisone and calcineurin inhibitors was effective in these patients [86]. One problem with this study is that it may not have had enough power given its small sample size of 31 patients, and it only had 3 months of follow-up at the time of publication. This study does emphasize the important clinical difference in those who respond to steroid treatment but are steroid-dependent and those who never respond to therapy. Steroid-resistant nephrotic syndrome in children remains a significant challenge. Though MCD is much less common in adults, RTX has been used with some success in case reports and small case series [87], [88] and [89]. FSGS is more common in the adult population and can be a challenge not only in the native kidney, but as recurrent disease in the renal allograft. The use of RTX in primary FSGS in adults has had variable, but mostly negative results in small case series [90], [91] and [92]. However, it may be useful in treating post-transplant relapse [93], [94] and [95]. Interestingly, recent research has shown that RTX may have a direct effect on podocytes, regardless of its action on B-cells, and this could explain the beneficial effect of RTX in these nephrotic disorders that are not clearly associated with auto-antibodies [96].

7. Concluding remarks

RTX has demonstrated considerable efficacy in treating several glomerular diseases. In ANCA-associated vasculitis, the RAVE and RITUXVAS trial demonstrated that RTX is as effective as cyclophosphamide in inducing remission in newly diagnosed cases and may be more effective in treating relapsing disease. Though the results of the LUNAR trial did not demonstrate a benefit for RTX in lupus nephritis, it still plays a role in refractory disease and in patients who cannot tolerate conventional therapy. In mixed cryoglobulinemia related to Hepatitis C, RTX is effective in treating both renal and extrarenal manifestations with few side effects and may limit the need for steroids as well. Studies on RTX in steroid-dependent MCD in children have shown improvement in proteinuria and an ability to be titrated off other medications; however, more recent data failed to show a benefit in children who are steroid-resistant. Current data do not support RTX in the treatment of primary FSGS in adults, but may be useful in recurrent disease in the renal allograft. Taken together, these trials all indicate that RTX is typically well-tolerated and carries a low risk of infection despite potent immunosuppression. RTX has become an indispensable addition to the treatment of glomerular diseases.

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